

Application 10/620,155

October 4, 2007 Reply to Office Action dated August 30, 2007

Attorney Docket P002.210

REMARKS/ARGUMENTS

I. Status of the claims

Upon entry of the present amendment, the specification was amended to correct typographical errors and delete unwanted text. Claims 1 through 22 are currently pending. In the June 5th, 2007 reply to the Office action dated May 11, 2007, Claims 24 and 25 were cancelled and claims 25 - 34 were withdrawn from consideration.

Claim 1 has been amended to overcome the indefiniteness rejection.

Claims 5 and 8 were amended to make ranges consistent with those used in the specification.

Claim 13 and 18 were amended to correct typographical errors.

Claim 21 was amended to depend from claim 20 which provides proper antecedent basis for the term "pump".

The amendments are fully supported by the application as filed and do not introduce new matter. Entry of these amendments is respectfully requested.

II. Examiner interview

Applicants thank Examiner Ramillano for the very productive telephone interview conducted on September 6, 2007. Present during the interview were Examiner Ramillano, Inventor, Douglas Gjerde and Applicant's representative, Sue Kalman. Several things were accomplished during the interview:

- 1) Applicants were able to understand the Examiner's assertions regarding the Colpan reference. Examiner Ramillano explained that she is applying the term "filter layer" used in Colpan's column 3 (lines 18 – 20) to the frits of the instant invention. In particular, the phrase "The particle size of the filter layer is in the range of from 5 microns to 500 microns" was discussed. Applicants explained that this phrase refers to the size of a particle within a packed bed that has a filtering function (element 20 in Colpan's figure). Examiner Ramillano maintained that she interpreted the phrase as referring to a structure comparable to Applicant's frit and requested that we put our arguments in writing for her consideration.

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- 2) To address the 35 U.S.C. 112, second paragraph rejection, amended language for claim 1 was discussed. Applicant's proposed removing the word "low" from claim 1 and Examiner Ramillano responded that the amendment would probably be fine.
- 3) Applicants cleared up the meaning of the term "Modified Hargro" used by Examiner Ramillano on pages 7, 8 and 9 of the Office action. The Examiner stated that the term "Modified Hargro" is another way of expressing Hargro in view of Colpan.

III. Claim rejections under 35 U.S.C. § 112

Claims 1 - 22 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically claim 1 was rejected as indefinite for use of the claim language "low pore volume". In response, claim 1 was amended to delete the term "low" as discussed with Examiner Ramillano during the September 6, 2007 telephonic interview. Since claims 2 - 22 depend from claim 1, withdrawal of the § 112 rejection is respectfully requested.

IV. Claim rejections under 35 U.S.C. § 102

Before addressing the individual rejections, Applicants would like to point out the significant differences between the instant invention and the invention of Colpan et al. ("Colpan", US 6,274,371), a reference cited by the Examiner in each § 102 and 103 rejection. In particular, Applicant's would like to elaborate in writing on one of the points discussed with Examiner Ramillano during the telephone interview on September 6, 2007. Examiner Ramillano interpreted the teachings of Colpan to include a column having a frit less than 350 microns thick. Applicants argued that Colpan does not teach a column having a frit less than 350 microns thick. In the paragraphs that follow, Applicants will discuss the differences between Colpan's filtration device and the low dead volume extraction column of the instant invention and explain our reading of the teachings of Colpan.

A. General comparison of Colpan and the instant invention

First, Applicants would like to compare very generally the device of Colpan with that of the instant invention. It is true that both are columns used to perform separations during the purification of cellular components from cells. However, the low dead volume extraction column of the instant invention differs from the filtration column of Colpan physically, chemically, functionally as well as in their respective intended purposes.

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It is often desirable to purify cellular components (e.g. nucleic acids and proteins) for analyses such as sequencing or mass spectrometry. The following three common steps are often performed for the purification of such cellular components.

- 1) Lyse the cells.
- 2) Separate the cell debris (solid) from the supernatant which contains the nucleic acids and proteins.
- 3) Purify the desired cellular component.

Step 1 can be performed using a variety of physical and chemical methods, some of which are listed by Colpan (column 1, lines 34-39).

Step 2 is usually accomplished by centrifugation. It is commonly known that centrifugation is not a highly specific separation method but rather a method that can be for separating liquids from solids. Colpan explains why centrifugation is an undesirable method for removal of cell fragments (column 1, lines 53-57) and describes their invention as filtration alternative to centrifugation. Filtration is defined as a mechanical process for separating a mixture of solids and fluids (<http://en.wikipedia.org/wiki/Filtration>, September 18, 2007). So Colpan's filtration is used to separate two different states of matter: liquid and solid. Colpan's filtration is not a specific separation used to isolate a specific biomolecule such as a particular protein from a cell.

The extraction columns of the instant invention do not have filtering function. Neither the frits nor the bed of extraction media act as a filter. A frit that acts as a filter is undesirable because the frit could become plugged, preventing or limiting the flow of sample components through the bed of extraction medium which in turn, could prevent the analyte from reaching the bed. In fact, Applicant's specification teaches away from frits acting as filters. "The performance of the column is typically enhanced by the use of frits having pore or mesh openings sufficiently large so as to minimize the resistance to flow." (page 26, lines 13 – 15). The fact that Applicants' specification teaches pore sufficiently large so as to minimize the resistance to flow supports the argument that filtering is not a desirable characteristic for the frits.

Step 3 is much more specific and usually involves techniques such as solid phase extraction or chromatography. The low dead volume columns of the instant invention are used for solid phase extraction, a step 3 process. Colpan acknowledges that their filtration process is preferably followed by further processing steps such as anion exchange or adsorption followed by desorption (column 2, lines 49-51). In fact, methods for using the extraction columns of the instant invention are precisely adsorption followed by desorption (e.g. claim 25). Solid phase extraction is a highly specific separation used to separate an analyte of interest from a complex solution. The extraction medium

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within the column can be chosen to purify a particular biomolecule such as a His-tagged protein or a monoclonal antibody (Table I of Applicant's specification). So while Colpan's column utilizes filtering to separate liquids from solids (step 2), the columns of the instant invention use solid phase extraction to purify a particular biomolecule such as an antibody (step 3).

In Colpan's filtration device, cell debris is retained while the liquid fraction containing nucleic acids flows through. To this end, Colpan teaches the use of materials that don't bind nucleic acids. In column 2, lines 16-17 Colpan writes "Preferably, the filter layers are modified such that there is no affinity for nucleic acids." In contrast, the extraction medium of the instant invention often has affinity for the desired analyte (Applicant's specification page 13, lines 25-34). The desired analyte binds an affinity group on the extraction medium while the remainder of the sample solution does not bind and flows through.

In addition, the input material for Colpan's filtering column is a mixture of solids and liquids. In contrast, the input material for the extraction columns of the instant invention is a liquid. Prior to using an extraction column of the instant invention, particulate matter such as cell debris is removed, usually by centrifugation. Although a small amount of particulate matter may remain after centrifugation, the input solution for extraction is a complex liquid solution rather than a mixture of liquids and solids.

The thin frits of the low dead volume extraction column of the instant invention are one of the most important elements of the instant invention. As Applicant's representative, Christopher Holman explained to Examiner Ramillano and Supervisor Gordon during the June 12th personal interview, thin frits confer upon the column a number of desirable properties. The frits have a low dead volume which contributes to the low dead volume of the extraction column. The low dead volume of the column facilitates the elution of a captured analyte in a very small volume of desorption solution, allowing for the preparation of small volume samples containing high concentrations of analyte. Additionally, the thin frits give the columns low back pressure, which in turn, allows for the use of gel resin media such as agarose. To Applicant's knowledge, frits less than 350 microns thick are not used in any other extraction column.

Frit thickness is not discussed for Colpan's filtration device. Colpan's drawing shows two elements labeled with reference number 23 that are described as "additional layer" in the "Brief Description of the Drawing" section (column 3, lines 21-25). Colpan gives only the following information regarding the function these elements.

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- *The filter layer is preferably arranged between two fixing means.*
(column 2, lines 53-54, bold emphasis added)
- *It may be advantageous to arrange an additional layer 23 in the hollow body 40, namely, above and/or below layer 20, which prevents premature penetration of the solution to be filtered into the filter, or leaking of the solution from the device according to the invention.*
(column 3, lines 21-25, bold emphasis added)
- *Where the hydrophobic separating layer 23 is arranged above separating layer 20, it is advantageous if the pore size of this separating layer is not smaller than that of underlying layer 20.*
(column 3, bold emphasis added)

B. Analysis of Colpan's column 3, lines 18-20

In the telephonic interview on September 6, 2007, Examiner Ramillano explained that she is applying the term "filter layer" used in Colpan's column 3 (lines 18 – 20) to the frits of the instant invention. In particular, she is applying the term "filter layer" from the phrase "The particle size of the filter layer is in the range of from 5 microns to 500 microns" to the frits disclosed in the instant invention. Applicants argued that this phrase refers to the size of a particle within a packed bed that has a filtering function (element 20 in Colpan's figure) and Examiner Ramillano maintained that she interpreted the phrase as referring to a structure comparable to Applicant's frit. Examiner Ramillano requested that we put our arguments in writing for her consideration.

Applicants raised this issue in the September 6th telephonic interview because thin frits are one of the novel features of the extraction columns of the instant invention. Frits less than 350 microns thick are recited in claim 1 and all claims under consideration depend from claim 1. Colpan is the sole reference relied upon by the Examiner to allegedly supply thin frits from the prior art so the question of whether or not Colpan teaches thin frits is of the utmost importance to this response. The sentence under discussion follows (column 3, lines 18 – 20, bold italics added).

The particle size of the filter layer is in the range of from 5 µm to 500 µm at a total thickness of the filter layer of from 0.1 to 200 mm.

In this sentence Colpan is stating the filter layer can be comprised of particles and a range of particle sizes is given. There are several lines of evidence supporting the fact that the above-sentence refers to the bed of particles labeled with reference no. 20 in Colpan's drawing rather than

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Colpan's additional layer which is labeled with reference no. 23 in the drawing. For simplicity, the elements labeled with reference numbers 20 and 23 in Colpan's drawing will be referred to as "element 20" and "element 23" hereinafter.

Granted, Colpan's use of terminology is inconsistent and confusing. However, based on Applicants careful reading of Colpan, it is evident that the above sentence refers to element 20 and not element 23. Colpan repeatedly uses the terms "filter layer" to refer to element 20. In fact Colpan uses the term "filter layer" 27 times. Colpan uses the simpler term "layer 20" 5 times and the term "separating layer 20" in only one instance. As noted with bold emphasis above, Colpan uses the term "filter layer" in the above sentence. For element 23, Colpan uses the terms "additional layer 23", "hydrophobic separating layer 23" and fixing means. However, Colpan never uses the term "filter layer" to refer to element 23.

Second, the sentence above is found in column 3, lines 18 through 20 of Colpan's patent. Element 23 is not introduced until column 3, line 21 so Colpan could not be referring to element 23 in lines 18 through 20.

Lastly, two parameters are associated with the single term, "filter layer" in the above sentence: particle size and thickness. Colpan teaches a particularly preferred embodiment in which the filter layer 20 is comprised of diatomaceous earth (column 2, lines 31 - 33) which is a particle so it is logical that a particle size would be associated with element 20. Further, it is reasonable that element 20 should possess both a thickness and a particle size however the same cannot be said for element 23. Element 23 would be expected to have a thickness but not a particle size.

In summary, Colpan does not teach a column with a frit less than 350 microns thick.

The following table summarizes some differences between the Colpan's invention and the extraction column of the instant invention.

Colpan	Instant invention
Method is filtration	Method is solid phase extraction
Purification step 2 (non-specific)	Purification step 3 (highly specific)
Column input is mixture of solids and liquids	Column input is liquid
Solids are retained	A biomolecule is adsorbed and later eluted
Does not posses frits < 350 µm thick	Has frits < 350 µm thick

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C. Claims anticipated by Colpan

In section 9 on page 4 of the Office action, the Examiner rejected claims 1,-3, 9, 10, 14, 15 and 19-22 as allegedly anticipated by Colpan et al. ("Colpan", US 6,274,371). In the second paragraph on page 9, the Examiner characterized Copan's invention as having "a column body (40)", "a bottom frit (23)", "a top frit (23)" and a "bed of extraction (20) media". Applicants interpret the use of the numbers in parentheses by the Examiner refers to the reference numbers used by Colpan to identify elements of their invention in the figure and BRIEF DESCRIPTION OF THE DRAWING section of column 3. By using the reference numbers in this manner the Examiner is asserting that the frits of the instant invention are comparable to element 23 in Colpan's drawing.

Applicants respectfully traverse the rejection. In order for a reference to be deemed anticipatory, it must disclose each element of the claims invention. Colpan fails to do this. In particular, Colpan fails to disclose frits less than 350 microns thick.

Claim 1 of the instant invention recites a low dead volume extraction column having frits that are less than 350 microns thick. In the personal interview conducted June 12th, 2007, Applicant's representative, Christopher Holman explained to Examiner Ramillano and Supervisor Gordon that the frit thickness is one of the novel features of the instant invention. To Applicant's knowledge, frits less than 350 microns thick are not used in any other extraction column.

The Examiner alleges that Colpan's invention has a top and bottom frit bonded to and extending across the open channel, that the top and bottom frits have a low pore volume and a thickness of less than 350 microns. Applicants respectfully disagree. In column 3, lines 21 - 32, Colpan gives only the following information with regard to element 23:

- above and/or below layer 20
- advantageous if the pore size of this separating layer is not smaller than that of underlying layer 20.
- prevents premature penetration of the solution to be filtered into the filter, or leaking of the solution from the device according to the invention

Colpan does not teach a frit that is less than 350 microns thick. Colpan says nothing about the thickness or pore volume of element 23. With respect to the Examiner's allegation that Colpan teaches frits bonded to the column, Colpan gives no information regarding the attachment of element 23 to the column body.

Although unlikely, it is possible that the Examiner's assertion that Colpan teaches a frit of less than 350 microns thick is based on the frits used in Examples 2 and 3 (column 3, line 67 to

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column 4, line 2 and column 4, lines 13 – 17). In these examples Colpan refers to a 50 μm PE frit. A person skilled in the art of building extraction columns knows that Colpan is using standard terminology to refer to a conventional frit having a pore size of 50 μm . Conventional frits such as those used in Examples 2 and 3 have a thickness of at least 1/16th inch and were shown to Examiner Ramillano and Supervisor Gordon during the June 12th personal interview with Applicant's representative, Christopher Holman. If necessary, a declaration under rule 37 C.F.R. § 1.132 can be supplied to address the nature of the 50 μm PE frits used in Examples 2 and 3.

Claim 10 is drawn to a nylon or polyester membrane screen frit. Claim 10 depends from claim 9 which in turn, depends from claim 1. So the nylon or polyester membrane screen frit of claim 10 must be less than 350 microns thick. In paragraph 3 of section 9, the Examiner contends that Colpan discloses a membrane screen that can be made of nylon or polyester. It is possible the Examiner is referring to the term "nylon net" is used in Example 2 (column 3, line 67 to column 4, line 2) as an alternative to a 50 μm PE frit. However, since Colpan gives no description of this nylon net, it cannot be concluded that the nylon net comprises a nylon membrane screen frit less than 350 μm thick. Based on the information provided in Example 2 we estimate the weight of the diatomaceous earth and liquid in the column to be at least one pound and it could be much more. Colpan gives no description of what a nylon net frit looks like, what it is, how a nylon net might be attached, assembled or supported in a column of this type, the number of layers of nylon net, or how this column might be assembled or used. In summary, it cannot be concluded that claim 10 is anticipated by Colpan.

So based on the arguments in this section and the section above entitled "Analysis of Colpan's column 3, lines 18-20", it is clear Colpan does not teach a column having frits less than 350 microns thick. Since Colpan does not teach frits less than 350 microns thick, claim 1 is not anticipated by Colpan. Since claims 2, 3, 9, 10, 14, 15 and 19-22 all depend from claim 1 and thus further limit claim 1, claims 2, 3, 9, 10, 14, 15 and 19-22 are not anticipated by Colpan. In view of the foregoing, Applicants respectfully request withdrawal of all of the rejections under 35 U.S.C. § 102.

V. Claim rejections under 35 U.S.C. § 103(a)

A. Brewer in view of Colpan et al.

In section 10 on page 5 of the Office action, the Examiner rejected claim 1 as allegedly obvious over Brewer (US 6566145) in view of Colpan. Applicants respectfully traverse the rejection on the grounds that the Examiner has not made a *prima facie* case of obviousness. The MPEP § 2143

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states "To establish a *prima facie* case of obviousness, the prior art reference, or references when combined, must teach or suggest all the claim limitations." Applicants respectfully submit that the references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness against claim 1 because neither Brewer nor Colpan teach or suggest frits less than 350 microns thick.

Brewer teaches a pipet tip-based mixing chamber for solid phase extraction. Claim 1 is drawn to a low dead volume extraction column having frits less than 350 microns thick. On page 5, paragraph 4 of the Office action, the Examiner states "Brewer does not specifically disclose a frit less than 350 microns thick."

On page 5, paragraph 5 the Examiner again quotes the following sentence from Colpan (column 3, lines 18 – 20, bold italics added).

*The particle size of the filter layer is in the range of from 5 µm to 500 µm
at a total thickness of the filter layer of from 0.1 to 200 mm.*

With regard to the above sentence the Examiner alleges "It would have been obvious to a person of ordinary skill in the art to modify Brewer's frits to have the specific filter dimensions as disclosed by Colpan because it would be desirable to have frits especially customized for microscale-sized chromatography columns".

As discussed above in the section entitled "Analysis of Colpan's column 3, lines 18-20", the above sentence does not teach frits less than 350 microns thick. Therefore the combination of Brewer and Colpan do not teach frits less than 350 microns thick.

In summary, Applicants respectfully submit that the references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness against the above-cited claims because neither Brewer nor Colpan, alone or in combination, teach or suggest each and every element of the claims. In particular neither Brewer nor Colpan, alone or in combination teach frits that are less than 350 microns thick. Therefore claim 1 is non-obvious. Since no *prima facie* case of obviousness over Brewer in view of Colpan has been established, withdrawal of the § 103 rejection is respectfully requested.

B. Hargro et al. in view of Colpan et al.

In section 12 on page 6 of the Office action, the Examiner rejected claims 1-6, 9-12, 14-15 and 18 - 22 as allegedly unpatentable over Hargro et al. ("Hargro", US 6,139,733) in view of Colpan. Again, Applicants respectfully traverse the rejection on the grounds that the Examiner has

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failed to establish a *prima facie* case of obviousness. Applicants respectfully submit that the references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness against the above-cited claims because neither Hargro nor Colpan teach or suggest frits less than 350 microns thick.

Hargro describes a column where sample is pre-adsorbed on media in the column by evaporating the solvent away. On page 7, paragraph 1 of the Office action, the Examiner states "Hargro does not specifically disclose a frit less than 350 or 200 microns thick; a frit having a pore volume of 1 microliter or less; and a membrane screen made of nylon." In the following paragraph the Examiner again quotes the following sentence from Colpan (column 3, lines 18 – 20, bold emphasis added).

The particle size of the filter layer is in the range of from 5 µm to 500 µm at a total thickness of the filter layer of from 0.1 to 200 mm.

The Examiner goes on to say "It would have been obvious to a person of ordinary skill in the art to modify Hargro's frits to have the specific filter dimensions as disclosed by Colpan because it would be desirable to have frits especially customized for microscale-sized chromatography columns".

As discussed above in the section entitled "Claims anticipated by Colpan", the Examiner is confusing Colpan's term "filter layer" with Applicant's term "frit". Claim 1 recites a low dead volume extraction column comprised of top and bottom frits that are less than 350 microns thick. Colpan does not teach a frit less than 350 microns thick. So neither Colpan nor Hargro teach a frit less than 350 microns thick. Therefore claim 1 is not obvious over Hargro in view of Colpan. Since claims 2-6, 9-12, 14-15 and 18 – 22 all depend from claim 1 (either directly or indirectly) and thus further limit claim 1, claims 2-6, 9-12, 14-15 and 18 – 22 are not obvious over in view of Colpan. Since no *prima facie* case of obviousness over Hargro in view of Colpan has been established, withdrawal of the § 103 rejection is respectfully requested.

C. Hargro et al. and Colpan et al. in view of Smith et al.

In section 13 on page 7 of the Office action, the Examiner rejected claims 7 and 13 as allegedly unpatentable over Hargro in view of Colpan, as applied to claims 1-6, 9-12, 14-15 and 18-22 above, and further in view of Smith et al. ("Smith", US Pub. No. 2004/0253687). Applicants respectfully traverse the rejection on the grounds that the Examiner has failed to make a *prima facie* case of obviousness. Applicants respectfully submit that the references cited by the Examiner are not

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sufficient to establish a *prima facie* case of obviousness against claim 1 because the combination of Hargro, Colpan and Smith does not teach or suggest a column having frits less than 350 microns thick.

Claim 7 is drawn to a low dead volume extraction column wherein the extraction media is comprised of agarose and sepharose. Claim 7 depends from claim 6 which depends from claim 1. Therefore the column of claim 7 must have frits less than 350 microns thick. Claim 13 recites a low dead volume extraction column, wherein the extraction media is comprised of an affinity binding group selected from the group consisting of Protein A, Protein G, Protein L and an immobilized metal. Claim 13 depends from claim 12 which in turn, depends from claim 1. Therefore the column of claim 13 must have frits less than 350 microns thick.

Smith teaches a method of purifying a plurality of proteins using conventional columns. The Examiner states that Smith uses a variety chromatography media including agarose, Sepharose and a Protein A affinity tag. The Examiner writes "It would have been obvious to a person of ordinary skill in the art to modify the modified Hargro by specifically utilizing sepharose or agarose since the modified Hargro discloses utilizing chromatography medium, which is a term commonly known in the art that pertains to gel-based chromatography media, such as agarose and cellulose. In addition, it would have been obvious to a person of ordinary skill in the art to modify the modified Hargro by specifically utilizing Protein A as the affinity tag because the modified Hargro discloses utilizing a media which is known in the art to contain materials that bind to an affinity tag of choice."

As mentioned above, the term "modified Hargro" refers to Hargro in view of Colpan. In this rejection, the Examiner is relying on modified Hargro to supply the frits less than 350 microns thick of claim 1. But as Applicants pointed out in the section above entitled "Hargro et al. in view of Colpan et al.", neither Hargro nor Colpan teach frits less than 350 microns thick. It follows that the chromatography media used by Smith is irrelevant because claims 7 and 13 depend from claim 1, and thus include the limitation of frits less than 350 microns thick and the combination of Hargro, Colpan and Smith does not teach or suggest frits less than 350 microns thick.

Since no *prima facie* case of obviousness over Hargro in view of Colpan and further in view of Smith has been established, withdrawal of the § 103 rejection is respectfully requested.

D. Hargro et al. and Colpan et al. in further view of Hunt et al.

In section 14 on page 8 of the Office action, the Examiner rejected claims 8 and 16 as allegedly unpatentable over Hargro in view of Colpan as applied to claims 1-6, 9-12, 14-15 and 18-22 above, and further in view of Hunt et al. Applicants note the citation of the Hunt reference was not

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supplied in the Office action or in the Notice of References cited. Applicants assume the Examiner is referring to US 2002/0110495 since that reference was present in the IDS submitted on December 7, 2005. Applicants respectfully request that the Examiner add the Hunt reference to the Notice of References Cited.

Applicants respectfully traverse the rejection on the grounds that the Examiner has not made a *prima facie* case of obviousness because the combination of Hargro, Colpan and Hunt does not teach all the elements of claims 8 and 16. Specifically, the combination of Hargro, Colpan and Hunt does not teach a low dead volume extraction column having frits less than 350 microns thick. Claim 8 is drawn to a low dead volume extraction column, wherein the bed of extraction media has a bed volume of less than 20 microliters. Claim 16 is drawn to a low dead volume extraction column, wherein the volume of the extraction media chamber is at most 1000 microliters. Since both claim 8 and claim 16 depend from claim 1 and thus further limit claim 1, the columns of claims 8 and 16 possess frits less 350 microns thick.

Hunt discloses a device for the purification and separation of substances (Abstract). The Examiner states that Hunt discloses a microcolumn with a single bed volume, 0.02 to 0.1 ml, and alleges that "It would have been obvious to a person of ordinary skill in the art to modify the modified Hargro by specifically having a bed volume of less than 20 microliters and an extraction media chamber at most 1000 microliters because it would be advantageous to utilize microscale-sized components for a microscale chromatography column."

First, as Applicants argued above, claim 1 is non-obvious over the modified Hargro (Hargro in view of Colpan) because the combination of Hargro and Colpan does not teach frits less than 350 microns thick. The addition of Hunt does not render claim 1 obvious. So the bed volume specified by Hunt is irrelevant because claims 8 and 16 depend from claim 1, and thus include the limitation of frits less than 350 microns thick and the combination of Hargro, Colpan and Smith does not teach or suggest frits less than 350 microns thick. Therefore, claims 8 and 16 are non-obvious.

Since no *prima facie* case of obviousness over Hargro in view of Colpan and in further view of Hunt has been established, withdrawal of the § 103 rejection is respectfully requested.

E. Hargro et al. and Colpan et al. in further view of Halmann et al.

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In section 15 on page 9 of the Office action, the Examiner rejected claim 17 as allegedly unpatentable over Hargro in view of Colpan as applied to claims 1-6, 9-12, 14-15 and 18-22 above, and further in view of Halmann et al. ("Halmann", US 4302534).

Applicants respectfully traverse the rejection on the grounds that the Examiner has not made a *prima facie* case of obviousness because the combination of Hargro, Colpan and Halmann does not teach all the elements of claim 17. Specifically, the combination of Hargro, Colpan and Halmann does not teach a low dead volume extraction column having frits less than 350 microns thick. Claim 17 is drawn to "the low dead volume extraction column of claim 1, wherein the bed of extraction media has a dry weight of less than 10 mg." Since claim 17 depends from claim 1 and thus further limit claim 1, the column of claim 17 possess frits less 350 microns thick.

Halmann teaches an enzymatic immunoassay, in which chemiluminescence is employed as a detection means. Halmann does not teach solid phase extraction. The Examiner refers to Example 2 in which a standard assay was developed for testing a solution for the presence of Staphylococcal Enterotoxin B (SEB). The assay involves mixing a solution to be tested with 0.05 ml of a suspension of anti-SEB-Sepharose (about 1 mg dry weight) in the presence of an SEB peroxidase conjugate in a test tube. After a 2-hour incubation and centrifugation, peroxidase bound to the Sepharose was determined according to the light emitted when hydrogen peroxide was added.

The Examiner writes "It would have been obvious to a person of ordinary skill in the art to modify the modified Hargro by specifically utilizing less than 10 mg dry weight of Sepharose because it would be beneficial to utilize a limited amount of chromatography media for microscale sized chromatography columns to insure a reasonable amount of chromatography media is packed inside the column".

First, the method of Example 2 cited by the Examiner does not include the use of an extraction column. Instead, the method is performed in test tubes. Second, as Applicants argued above, claim 1 is non-obvious over the modified Hargro (Hargro in view of Colpan) because the combination of Hargro and Colpan does not teach frits less than 350 microns thick. The addition of Halmann does not render claim 1 obvious. So the dry weight disclosed by Halmann is irrelevant because claim 17 depends from claim 1, and thus includes the limitation of frits less than 350 microns thick. The combination of Hargro, Colpan and Halmann does not teach or suggest frits less than 350 microns thick. Therefore, claim 17 is non-obvious.

Since no *prima facie* case of obviousness over Hargro in view of Colpan and in further view of Halmann has been established, withdrawal of the § 103 rejection is respectfully requested.

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CONCLUSION

Applicants believe no fee is required for submission of this response, however, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 50-2852.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner seeks to maintain the rejections, Applicant requests a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (408)267-7214.

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